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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 09/941,992 | 08/28/2001 | Avi J. Ashkenazi | P2730P1C1 | 8312 |

30313 7590 10/12/2005

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| **ART UNIT** | **PAPER NUMBER** |
| 1646 | |

DATE MAILED: 10/12/2005

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**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

Application Number: 09/941,992
Filing Date: August 28, 2001
Appellant(s): ASHKENAZI ET AL.

Daphne Reddy
For Appellant

**EXAMINER'S ANSWER**

This is in response to the appeal brief filed 27 July 2005 appealing from the Office action mailed 16 September 2004.

**(1) Real Party in Interest**

A statement identifying by name the real party in interest is contained in the brief.

**(2) Related Appeals and Interferences**

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

09/991,150 (also on appeal)

09/990,711 (notice of appeal filed).

**(3) Status of Claims**

The statement of the status of claims contained in the brief is essentially correct. In the amendment of 27 October 2003, claim 130 was also amended.

**(4) Status of Amendments After Final**

The appellant's statement of the status of amendments after final rejection contained in the brief is incorrect.

The amendment after final rejection filed on 27 January 2005, requesting a change in inventorship under 37 C.F.R. § 1.48(b) has been entered.

**(5) Summary of Claimed Subject Matter**

The summary of claimed subject matter contained in the brief is correct. Of course, the examiner disagrees with the statements regarding the significant overexpression of PRO341 in certain cancers for reasons explained herein.

**(6) Grounds of Rejection to be Reviewed on Appeal**

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

**(7) Claims Appendix**

The copy of the appealed claims contained in the Appendix to the brief is correct.

**(8) Evidence Relied Upon**

Sen, 2000, Curr. Opin. Oncol. 12:82-88.

Hittelman, 2001, Ann. NY Acad. Sci. 952:1-12.

Pennica et al., 1998, PNAS USA 95:14717-14722.

Konopka et al., Proc. Natl. Acad. Sci. (1986) 83:4049-4052.

Chen et al., 2002, Molecular and Cellular Proteomics 1:304-313.

Hu et al., 2003, Journal of Proteome Research 2:405-412.

LaBaer, 2003, Nature Biotechnology 21:976-977.

Haynes et al., 1998, Electrophoresis 19:1862-1871.

Gygi et al., 1999, Mol. Cell. Biol. 19:1720-1730.

Lian et al., 2001, Blood 98:513-524.

Fessler et al., 2002, J. Biol. Chem. 277:31291-31302.

**(9) Grounds of Rejection**

The following ground(s) of rejection are applicable to the appealed claims:

Claims 124-126 and 129-131 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility.

The claims are directed to isolated polypeptides comprising the amino acid sequence of SEQ ID NO: 20 with or without its signal peptide, or comprising the amino acid sequence of the full-length coding sequence of the cDNA deposited under ATCC accession number 209792. Claims are also presented to chimeric proteins comprising the aforementioned polypeptides. The specification teaches that the polypeptide of SEQ ID NO: 20, also known as PRO341, is a membrane-bound polypeptide with several transmembrane domains. The specification does not disclose that PRO341 has significant structural similarity to any fully characterized polypeptides. There is no biological activity, expression pattern, phenotype, disease or condition, ligand, binding partner, or any other specific feature that is disclosed as being associated with PRO341. Without any information as to the specific properties of PRO341, the mere identification of such as being a membrane-bound polypeptide possessing several transmembrane domains is not sufficient to impart a well-established utility to the claimed polypeptides. The specification contains numerous asserted utilities for PRO341, including use as molecular weight markers, therapeutic agents, and for the production of antibodies. None of these asserted utilities is specific for the disclosed PRO341 polypeptide, as each of the aforementioned utilities could be asserted for any naturally occurring polypeptide, and further, as none of the asserted utilities requires any feature or activity that is specific to the disclosed PRO341.

At pages 539-555, a gene amplification assay discloses that genomic DNA encoding PRO341 had a ΔCt value of at least 1.0 for three out of fourteen lung tumor samples. Genomic DNA encoding PRO341 was not amplified in any of the fourteen

colon tumor samples. At page 548, ΔCt is defined as the threshold PCR cycle, or the cycle at which the reporter signal accumulates above the background level of fluorescence. The specification further indicates that ΔCt is used as "a quantitative measurement of the relative number of starting copies of a particular target sequence in a nucleic acid sample when comparing cancer DNA results to normal human DNA results." It is noted that at page 548, it is stated that samples are used if their values are within 1 Ct of the 'normal standard'. It is further noted that the ΔCt values at pages 550-554 are expressed (a) with values to one one-hundredth of a unit (e.g. 2.58), and (b) that very few values were obtained that were at least 2. Given the paucity of information, the data do not support the implicit conclusion of the specification that PRO341 genomic DNA shows a positive correlation with lung cancer, much less that the levels of PRO341 genomic DNA would be diagnostic of such. Cancerous tissue is known to be aneuploid, that is, having an abnormal number of chromosomes (see Sen, 2000, Curr. Opin. Oncol. 12:82-88). The data presented in the specification were not corrected for aneuploidy. A slight amplification of a gene does not necessarily correlate with overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid. Furthermore, the literature reports that lung epithelium is at risk for cellular damage due to direct exposure to environmental pollutants and carcinogens, which result in aneuploidy *before* the epithelial cells turn cancerous. See Hittelman (2001, Ann. NY Acad. Sci. 952:1-12; cited in related PRO341 applications), who teach that damaged, precancerous lung epithelium is often aneuploid. See especially p. 4, Figure 4. The gene amplification assay in the specification does not provide a direct

comparison between the lung tumor samples and normal lung epithelium. Rather, the assay discloses amplification of PRO341 genomic DNA in lung tumors compared to "normal human DNA" (apparently from blood samples), and thus a skilled artisan would not conclude that PRO341 genomic DNA is amplified in cancerous lung epithelium more than in damaged (non-cancerous) lung epithelium. One skilled in the art would not conclude that PRO341 genomic DNA is a diagnostic probe for lung cancer unless it is clear that PRO341 genomic DNA is amplified to a clearly greater extent in true lung tumor tissue relative to non-cancerous lung epithelium. Also, while it might be argued in hindsight that PRO341 would still be a marker at least for precancerous, or damaged, lung epithelium, such is not suggested by the specification as originally filed and is not well-established in the prior art.

Moreover, the data for PRO341 genomic DNA have no bearing on the utility of the claimed PRO341 polypeptides. In order for PRO341 polypeptides to be overexpressed in lung tumors, amplified genomic DNA would have to correlate with amplified mRNA, which in turn would have to correlate with amplified polypeptide levels. The art discloses that such correlations cannot be presumed. Regarding the correlation between genomic DNA amplification and increased mRNA expression, see Pennica et al. (1998, PNAS USA 95:14717-14722), who disclose that:

> "An analysis of *WISP*-1 gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of *WISP*-3 RNA was seen in the absence of DNA amplification. In contrast, *WISP*-2 DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient."

See p. 14722, second paragraph of left column; pp. 14720-14721, "Amplification and Aberrant Expression of *WISPs* in Human Colon Tumors." See also Konopka et al. (Proc. Natl. Acad. Sci. (1986) 83:4049-4052), who state that "Protein expression is not related to amplification of the abl gene but to variation in the level of bcr-abl mRNA produced from a single Ph1 template" (see abstract). Even if increased mRNA levels could be established for PRO341, it does not follow that polypeptide levels would also be amplified. Chen et al. (2002, Molecular and Cellular Proteomics 1:304-313) compared mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas. Only 17% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen et al. clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (p. 304) and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pp. 311-312). Also, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). One of the authors of this paper, Dr. LaBaer, made an even

stronger statement that reports of mRNA or protein changes of as little as two-fold are not uncommon, and although changes of this magnitude may turn out to be important, **most** are attributable to disease-independent differences between the samples (emphasis added; 2003, Nature Biotechnology 21:976-977).

The art also shows that transcript levels do not correlate with polypeptide levels in normal tissues. See Haynes et al. (1998, Electrophoresis 19:1862-1871), who studied more than 80 polypeptides relatively homogeneous in half-life and expression level, and found no strong correlation between polypeptide and transcript level. For some genes, equivalent mRNA levels translated into polypeptide abundances which varied more than 50-fold. Haynes et al. concluded that the polypeptide levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Gygi et al. (1999, Mol. Cell. Biol. 19:1720-1730) conducted a similar study with over 150 polypeptides. They concluded that

> "the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data. Indeed, for some genes, while the mRNA levels were of the same value the protein levels varied by more than 20-fold. Conversely, invariant steady-state levels of certain proteins were observed with respective mRNA transcript levels that varied by as much as 30-fold. Our results clearly delineate the technical boundaries of current approaches for quantitative analysis of protein expression and reveal that simple deduction from mRNA transcript analysis is insufficient"

(See Abstract). Lian et al. (2001, Blood 98:513-524) show a similar lack of correlation in mammalian (mouse) cells (see p. 514, top of left column: "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be

difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels."). See also Fessler et al. (2002, J. Biol. Chem. 277:31291-31302) who found a "[p]oor concordance between mRNA transcript and protein expression changes" in human cells (p. 31291, abstract).

Therefore, data pertaining to PRO341 genomic DNA do not indicate anything significant regarding the claimed PRO341 polypeptides. The data do not support the specification's assertion that PRO341 polypeptides can be used as a cancer diagnostic agent. Significant further research would have been required of the skilled artisan to reasonably confirm that PRO341 is overexpressed in any cancer to the extent that it could be used as a cancer diagnostic agent, and thus the asserted utility is not substantial. In the absence of information regarding whether or not PRO341 polypeptide levels are also different between specific cancerous and normal tissues, the proposed use of the PRO341 **polypeptides** as diagnostic markers and therapeutic targets are simply starting points for further research and investigation into potential practical uses of the polypeptides. See Brenner v. Manson, 148 U.S.P.Q. 689 (Sup. Ct., 1966), wherein the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Claims 124-126 and 129-131 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

**(10) Response to Argument**

At the middle of p. 4 of the Brief, Appellant argues that the patentable utility of PRO341 polypeptides is based on the gene amplification data for the gene encoding the PRO341 polypeptide. Appellant states that the specification shows significant amplification of the gene encoding PRO341 in three different lung tumors. Appellant refers to the declaration of Dr. Goddard (submitted under 37 C.F.R. § 1.132 on 24 October 2003) as explaining that a gene that is amplified at least 2-fold by the disclosed gene amplification assay in a tumor sample relative to a normal sample is useful for the diagnosis of cancer, for monitoring cancer development, and/or for measuring the efficacy of cancer therapy. Appellant concludes that one of ordinary skill in the art would find it credible that the claimed PRO341 polypeptides have utility as markers for the diagnosis of lung tumors. This has been fully considered but is not found to be persuasive for the following reasons. The specification shows that PRO341 genomic DNA was amplified in only three out of fourteen lung tumor samples as compared to a normal human DNA control that was apparently isolated from blood. One skilled in the art would conclude that it was more likely that PRO341 genomic DNA is *not* amplified in

any given lung tumor sample based on those results. Furthermore, the data are not based on direct comparison of amplification levels between lung tumor and healthy lung. Comparison of matched tissue samples is considered the standard in the cancer diagnosis art. See Hu et al., of record, for instance. Finally, the art indicates that gene amplification data do not correlate with increased mRNA levels or increased polypeptide levels (see Pennica et al., Konopka et al., Haynes et al., Gygi et al., Lian et al., Fessler et al., Hu et al., LaBaer, Chen et al.). Since the instant claims are directed to polypeptides, this is a major concern. The Goddard declaration was not found to be sufficient to overcome the rejection; however, the Goddard declaration will be addressed at length later in this answer.

At p. 5 of the Brief, Appellant argues that the combined teachings of Pennica et al. and Konopka et al. are not directed to genes in general but to a single gene or genes within a single family. Appellant urges that their teachings cannot support a general conclusion regarding correlation between gene amplification and mRNA or polypeptide levels. Appellant argues that Orntoft et al., Hyman et al. and Pollack et al. teach that, in general, gene amplification increased mRNA expression. Appellant points to the Polakis declaration (submitted under 37 C.F.R. § 1.132 on 07 July 2004) as establishing that there is a general correlation between mRNA levels and polypeptide levels. Appellant notes that the sale of gene expression chips to measure mRNA levels is a highly successful business. Appellant asserts that the research community believes that the information obtained from these chips is useful. Finally, Appellant concludes that, while there may be exceptions, there is generally a good correlation between gene

amplification, mRNA levels and polypeptide levels, and thus the gene amplification data for PRO341 conveys utility to the claimed PRO341 polypeptides. This has been fully considered but is not found to be persuasive. While Pennica et al. and Konopka et al. are directed to small numbers of genes, the instant application concerns only one gene as well. Furthermore, Haynes et al., Gygi et al., Lian et al., Fessler et al., Hu et al., Chen et al., and LaBaer all speak to larger sets of genes and constitute evidence that polypeptide levels cannot be predicted from mRNA levels in general. The Polakis declaration will be addressed in detail later in this answer. Regarding gene chips, it is submitted that evidence of financial success is not relevant to utility or enablement. Also, the chips may provide useful information about genes, but not polypeptides. Finally, products that provide only potential or preliminary results may also sell well in the research community since the researcher who buys them may plan to follow up any preliminary results obtained from the chips with experiments directed at measuring polypeptide levels.

In the paragraph bridging pp. 5-6 of the Brief, Appellant argues that, even if there were no correlation between gene amplification and increased mRNA/polypeptide expression, a polypeptide encoded by a gene that is amplified in cancer would still have utility in that simultaneous testing of gene amplification and gene product overexpression enables more accurate tumor classification, leading to a better determination of a suitable therapy, as demonstrated by the real-world example of the breast cancer marker HER-2/neu. Appellant points to the Ashkenazi declaration (submitted under 37 C.F.R. § 1.132 on 24 October 2003) and Hanna et al. as

supporting this point. This has been fully considered but is not found to be persuasive, since the specification does not disclose that the PRO341 polypeptide levels increase **or** stay the same. Further research would be needed to determine PRO341 polypeptide levels in cancers showing gene amplification of PRO341 gene. Therefore, the asserted utility is not substantial, as the real-world use has not been established. The proposed use of the PRO341 polypeptides as claimed in this application are simply starting points for further research and investigation into potential practical uses of the polypeptides. The Ashkenazi declaration (submitted under 37 C.F.R. § 1.132 on 24 October 2003) will be addressed in detail later in this answer. The Hanna et al. reference actually supports the rejection, since Hanna et al. show that gene amplification does not reliably correlate with polypeptide overexpression, and thus the level of polypeptide expression must be tested empirically. The specification does not provide this further information, and thus the skilled artisan must perform additional experiments. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial.

At the middle of p. 6 of the Brief, Appellant argues that, since PRO341 polypeptides have utility in the diagnosis of cancer, they are also enabled. Appellant urges that the skilled artisan would know how to use the claimed polypeptides in cancer diagnosis based on the disclosure. This has been fully considered but is not found to be persuasive since the PRO341 polypeptides have no utility for the reasons set forth in the rejection under 35 U.S.C. § 101, above, they also are not enabled.

At pp. 7-8 of the Brief, Appellant reviews the legal standard for utility, with which the examiner takes no issue.

At p. 9 of the Brief, Appellant argues that the data in Example 170 (starting at p. 539 of the specification) describes results of a gene amplification assay. Appellant characterizes the assay as being capable of quantitatively measuring the level of gene amplification in a sample. Appellant asserts that gene amplification is an essential mechanism for oncogene activation. Appellant reviews how the assay was performed, and reports that the gene encoding PRO341 was significantly amplified (2.173-fold to 2.514-fold) in three lung tumors. This has been fully considered but is not found to be persuasive. First, it is important to note that the gene encoding PRO341 was not found to be amplified in eleven out of fourteen lung tumor samples, and also was not found to be amplified in any colon tumor samples. Also, matched tissue samples were not used for controls. Rather, the control DNA appears to have been isolated from blood (bottom of p. 547). The art uses matched tissue samples as the standard in such cases (see Pennica et al., Konopka et al.). This is especially important in lung, since the art shows that both cancerous and non-cancerous lung tissue can be aneuploidy (see Sen, Hittelman). Given these details, one skilled in the art would not conclude that the gene encoding PRO341 would be useful as a cancer diagnostic or a target for cancer drug development, but would rather view the data as preliminary results. Furthermore, the data pertaining to gene amplification do not convey utility to the claimed polypeptides, since a small amplification in genomic DNA is shown in the art to fail to correlate with a

corresponding increase in mRNA and polypeptide levels (see Pennica et al., Konopka et al., Haynes et al., Gygi et al., Lian et al., Fessler et al., Hu et al., LaBaer, Chen et al.).

From p. 9 to p. 10 of the Brief, Appellant refers to the declaration of Dr. Goddard, submitted under 37 C.F.R. § 1.132 on 24 October 2003. Appellant quotes from p. 3 of the declaration as giving an expert opinion that a 2-fold increase in gene copy number in a tumor sample relative to a non-tumor sample is significant and useful. Appellant concludes that one skilled in the art would consider the 2.173 to 2.514-fold amplification of the gene encoding PRO341 in three lung tumors is significant and credible based upon the facts in the Goddard declaration. This has been fully considered but is not found to be persuasive. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant situation, the nature of the fact sought to be established is whether or not a 2.173 to 2.514-fold amplification of the gene encoding PRO341 in three lung tumors is significant and credible. Credibility has never been questioned. However, the significance can be questioned since eleven of the fourteen lung tumor samples did not show an amplification of the gene encoding PRO341, and the control used was not a matched non-tumor lung sample but rather was a pooled DNA sample from blood of

healthy subjects. The art uses matched tissue samples (see Pennica et al., Konopka et al.). Hu et al. and Chen et al. speak to the strength of the opposing evidence, as do Pennica et al., Konopka et al., Haynes et al., Gygi et al., Lian et al., and Fessler et al., discussed in the rejection above. The expert has interest in the outcome of the case since Dr. Goddard is listed as an inventor and is employed by the assignee. Finally, the expert refers to three publications as factual support for the conclusions in the declaration. However, neither Livak et al. nor Heid et al. appear to indicate that an approximately 2-fold amplification of genomic DNA is significant in tumors. Pennica et al. was found to support the rejection, as discussed in the rejection above. The Goddard declaration evinces that the instant specification provides a mere invitation to experiment, and not a readily available utility. The PRO341 gene has *not* been associated with tumor formation or the development of cancer, nor has it been shown to be predictive of such. Similarly, the PRO341 gene has *not* been shown to be useful to track the efficacy of cancer therapy. The specification merely demonstrates that the PRO341 genomic DNA may be amplified in some cancers, to a minor degree (about 2.5 fold) compared to normal DNA from blood. No mutation or translocation of PRO341 has been associated with any type of cancer versus normal tissue. It is not known whether PRO341 is amplified in corresponding normal tissues, and what the relative levels of amplification are. In the absence of any of the above information, all that the specification does is present evidence that the DNA encoding PRO341 may be amplified in a variety of samples and invites the artisan to determine the significance of this increase. It remains that, as evidenced by Pennica et al., the issue is simply not

predictable, and the specification presents a mere invitation to experiment. Based on consideration of the evidence as a whole, the rejection is proper.

In the second paragraph of p. 10 of the Brief, Appellant argues that it is well known that gene amplification occurs in most solid tumors, including lung carcinomas, and is generally associated with poor prognosis. Appellant concludes that the PRO341 gene becomes an important diagnostic marker to identify malignant lung carcinomas, even when the lung malignancy associated with PRO341 molecule is a rare occurrence. This has been fully considered but is not found to be persuasive. As discussed in the rejection above, gene amplification is common in non-cancerous lung epithelium based on the damage the epithelium suffers from exposure to the environment. See Sen and Hittelman et al. There is no control for non-cancerous lung tissue, and thus the relevance of the data in the specification is not clear. Furthermore, there is no disclosure of a correlation of amplification with tumor formation, progression, severity, etc., all of which would speak to prognosis.

In the third paragraph of p. 10 of the Brief, Appellant quotes the specification regarding amplification being associated with overexpression of the gene product, indicating that polypeptides are useful targets for therapeutic intervention in certain cancers. This has been fully considered but is not found to be persuasive, since this assertion is completely unsupported by any evidence, and the art provides evidence to the contrary. Specifically, Pennica et al. (1998, PNAS USA 95:14717-14722), show a lack of correlation between gene amplification and overexpression in two out of three WISP genes. Konopka et al. (Proc. Natl. Acad. Sci. (1986) 83:4049-4052) state that

polypeptide expression correlated with mRNA levels, but not gene amplification for the abl gene. Even if increased mRNA levels could be established for PRO341, it does not follow that polypeptide levels would also be amplified. Chen et al. (2002, Molecular and Cellular Proteomics 1:304-313) compared mRNA and polypeptide expression for a cohort of genes in the same lung adenocarcinomas. Only 17% of 165 polypeptide spots or 21% of the genes had a significant correlation between polypeptide and mRNA expression levels. Chen et al. clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (p. 304) and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pp. 311-312). Also, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). One of the authors of this paper, Dr. LaBaer, made an even stronger statement that reports of mRNA or protein changes of as little as two-fold are not uncommon, and although changes of this magnitude may turn out to be important, **most** are attributable to disease-independent differences between the samples (emphasis added; 2003, Nature

Biotechnology 21:976-977). Finally, the art also shows that transcript levels do not correlate with polypeptide levels in normal tissues. See Haynes et al. (1998, Electrophoresis 19:1862-1871), who studied more than 80 polypeptides relatively homogeneous in half-life and expression level, and found no strong correlation between polypeptide and transcript levels. For some genes, equivalent mRNA levels translated into polypeptide abundances which varied more than 50-fold. Haynes et al. concluded that the polypeptide levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Gygi et al. (1999, Mol. Cell. Biol. 19:1720-1730) conducted a similar study with over 150 polypeptides. They concluded that

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(See Abstract). Lian et al. (2001, Blood 98:513-524) show a similar lack of correlation in mammalian (mouse) cells (see p. 514, top of left column: "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels."). See also Fessler et al. (2002, J. Biol. Chem. 277:31291-31302) who found a "[p]oor concordance between mRNA transcript and protein expression changes"

in human cells (p. 31291, abstract).

At the bottom of p. 10 to the top of p. 11 of the Brief, Appellant refers to Orntoft et al., Hyman et al., and Pollack et al. as evidence supporting the assertion that gene amplification more likely than not correlates with increased polypeptide levels. Appellant characterizes Orntoft et al. as studying transcript levels of 5600 genes in malignant bladder cancers, many of which were linked to the gain or loss of chromosomal material and found that in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. Appellant characterizes Hyman et al. as comparing DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, and found that there was evidence of a prominent global influence of copy number changes on gene expression levels. Appellant characterizes Pollack et al. as profiling DNA copy number alteration across 6691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines, and found that one average, a 2-fold change in DNA copy number was associated with a corresponding 1.5-fold increase in mRNA levels. Appellant concludes that gene amplification is more likely than not predictive of increased mRNA and polypeptide levels. This has been fully considered but is not found to be persuasive. Orntoft et al. (Molecular and Cellular Proteomics 1:37-45, 2002) could only compare the levels of about 40 well-resolved and focused *abundant* proteins." (See abstract.) It would appear that Appellants have provided no fact or evidence concerning a correlation between the specification's disclosure of *low* levels of amplification of DNA (which were not characterized on the basis of those in the

Orntoft publication) and an associated rise in level of the encoded protein. Hyman (Cancer Research 62:6240-6245) found 44% of *highly* amplified genes showed overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes were amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO341 would be correlated with elevated levels of mRNA, much less protein. Hyman does not examine protein expression. Pollack et al. is similarly limited to highly amplified genes which were not evaluated by the method of the instant specification. None of the three references are directed to gene amplification, mRNA levels, or polypeptide levels in lung cancer.

At the middle of p. 11 of the Brief, Appellant refers to the declaration of Dr. Polakis, submitted under 37 C.F.R. § 1.132 with the response filed 07 July 2004. Appellant characterizes the declaration as setting forth Dr. Polakis' experience with microarray analysis wherein approximately 200 gene transcripts present in human tumor cells were found to be at significantly higher levels than in corresponding normal human cells. The declaration goes on to state that antibodies binding to about 30 of these tumor antigens were prepared, and mRNA and protein levels compared. The declaration states that in approximately 80% of the cases, the researchers found that increased levels of RNA correlated with changes in the level of protein. Appellant

concludes that all of the submitted evidence supports Appellant's position that it is more likely than not that increased gene amplification levels predict increased mRNA and increased protein levels, thus meeting the utility standards. This has been fully considered but is not found to be persuasive. As discussed above, in assessing the weight to be given expert testimony, the examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. (1) In the instant case, the nature of the fact sought to be established is whether or not gene amplification is predictive of increased mRNA levels and, in turn, increased protein levels. Dr. Polakis declares that 80% of approximately 200 instances of elevated mRNA levels were found to correlate with increased protein levels. (2) It is important to note that the instant specification only discloses gene amplification data for PRO341 (i.e., data regarding amplification of PRO341 genomic DNA), and does not disclose any information regarding PRO341 mRNA levels. Furthermore, there is strong opposing evidence showing that gene amplification is not predictive of increased mRNA levels in normal and cancerous tissues and, in turn, that increased mRNA levels are frequently not predictive of increased polypeptide levels. See, e.g., Pennica et al., Konopka et al., Chen et al. (who found only 17% of 165 polypeptide spots or 21% of the genes had a significant correlation between polypeptide and mRNA expression levels in lung adenocarcinoma samples), Hu et al. (who reviewed 2286 genes reported in the literature to be associates with breast cancer), LaBaer, Haynes et al., Gygi et al., Lian et

al., and Fessler et al., all discussed *supra*. (3) Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Polakis is employed by the assignee. (4) Finally, Dr. Polakis refers to facts; however, the data is not included in the declaration so that the examiner could not independently evaluate them. For example, how many of the tumors were lung tumors? How highly amplified were the genes that correlated with increased polypeptide levels?

In the section bridging pp. 11-12 of the Brief, Appellant refers to the declaration of Dr. Ashkenazi, submitted under 37 C.F.R. § 1.132 with the response of 24 October 2003. In the declaration, Dr. Ashkenazi states that, even when amplification of a cancer marker gene does not result in significant overexpression of the corresponding gene product, the absence of gene product overexpression still provides significant information for cancer diagnosis and treatment. Appellant also refers to Hanna et al., submitted with the response of 7 July 2004, in which breast cancer diagnosis includes testing for HER-2/neu amplification and absence of HER-2/neu gene product overexpression. Appellant argues that such leads to a more accurate classification of the cancer and a more effective way of treating it. Appellant argues that the PRO341 polypeptide is also useful in tumor categorization (such as suggested by the Ashkenazi declaration and the Hanna et al. reference), the results of which become an important tool in the hands of a physician enabling the selection of treatment modality that holds the most promise for the successful treatment of a patient. This has been fully considered but is not found to be persuasive. While it may be true that lack of overexpression of a gene product can also provide useful information in tumor

categorization, the specification does not disclose such further testing of PRO341 gene product expression levels. Therefore, the skilled artisan would have been required to do the testing. In view of such requirement, the products based on the claimed invention are not in "currently available" form. Furthermore, the specification provides no assertion that the claimed PRO341 polypeptides are useful in tumor categorization, nor does it provide guidance regarding what treatment modalities should be selected by a physician depending upon whether or not a tumor overexpresses PRO341. This is also further experimentation that would have to be performed by the skilled artisan, indicating that the asserted utility is not substantial. Finally, Hanna et al. supports the rejection, in that Hanna et al. show that gene amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested empirically. The specification does not provide this further information, and thus the skilled artisan must perform additional experiments to reasonably confirm the real world context of the asserted utility. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial.

At the bottom of p. 12 to the middle of p. 13 of the Brief, Appellant concludes that, based on the gene amplification data presented for PRO341, there is ample support for the Appellant's position that increased gene amplification levels more likely than not predict increased mRNA and polypeptide levels. Appellant urges that one skilled in the art would reasonably expect, based on the gene amplification date, declarations, and supportive articles presented by Appellant that the PRO341 polypeptide is most likely to be concomitantly overexpressed in certain lung tumors and

is therefore useful as a lung cancer marker. Appellant argues further that even if PRO341 polypeptide was not overexpressed in lung tumors, PRO341 polypeptide would still be useful as a marker in tumor categorization and becomes a useful tool enabling the physician to decipher appropriate lines of treatment for the cancer patients. This has been fully considered but is not found to be persuasive for four reasons. First, PRO341 genomic DNA was found to be amplified in only three out of fourteen lung cancer samples compared to a normal DNA control from blood. Gene amplification in lung tumors was not compared to a matched normal tissue sample, as is the standard in the art (see Pennica et al., Konopka et al.). The data were not corrected for aneuploidy, which was known to be common in cancerous and non-cancerous lung tissue (see Sen, Hittelman). Thus, it is not clear from the gene amplification data whether or not PRO341 genomic DNA actually is amplified in certain lung tumors. Second, the literature reports that gene amplification often does not correlate with increased mRNA levels (see Pennica et al., Konopka et al.). Third, the literature reports that increased mRNA levels do not correlate with increased polypeptide levels in healthy tissue (see Haynes et al., Gygi et al., Lian et al., Fessler et al.) or cancerous tissue (see Hu et al., LaBaer, Chen et al., Hanna et al.). In view of the totality of the evidence, the skilled artisan would not reasonably presume that PRO341 polypeptide is overexpressed in certain lung tumors based on the disclosure regarding gene amplification without actually testing for PRO341 polypeptide overexpression. The requirement for such testing indicates that the asserted utility is not substantial, i.e., it is not in currently available form. Fourth, based on the gene amplification data, the skilled artisan *also*

would not presume that PRO341 polypeptide is *not* overexpressed in certain lung tumors without actually testing for PRO341 polypeptide levels. In view of such and the lack of guidance regarding how the physician would use information regarding PRO341 polypeptide overexpression, or lack of overexpression, in categorizing a tumor and choosing a treatment modality, the asserted utility for PRO341 polypeptide as a cancer diagnostic is not substantial. In view of the totality of the evidence, the rejections for lack of utility and enablement are proper.

At pp. 13 to the top of p. 14 of the Brief, Appellant argues that the asserted utility for PRO341 as a cancer diagnostic is credible and specific. The examiner agrees.

From the middle of p. 14 to the middle of p. 15 of the Brief, Appellant argues that the requirement for an asserted utility to be "substantial" means that the claimed invention must have a "practical purpose" which is not a throw-away or insubstantial use, such as the use of a complex invention as landfill. Appellant quotes from M.P.E.P. § 2107 regarding the requirement for a substantial asserted utility. Appellant argues that they have demonstrated at least one reasonable use for the PRO341 polypeptide as a diagnostic marker for detecting or at least classifying lung carcinomas. Appellant urges that such uses serve a practical purpose which is not a throw-away or insubstantial use. Appellant also objects to the examiner's characterization of the gene amplification as "preliminary data," stating that there is ample support for the Appellant's position that increased gene amplification levels more likely than not predict increased mRNA and polypeptide levels. This has been fully considered but is not found to be persuasive. M.P.E.P. § 2107 I states:

> A "substantial utility" defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities.

In the instant case, the asserted utility that PRO341 polypeptides are useful as diagnostic markers for cancer is not substantial in that further research is required to reasonably confirm a real world context of use. In order for PRO341 polypeptide to be useful as a cancer diagnostic, there must be a detectable change in the amount or form of PRO341 polypeptide between cancerous and healthy tissue. In the instant case, the evidence of record indicates that (1) the initial gene amplification assay only showed a positive result for three out of fourteen lung cancer sample, and did not take into account aneuploidy in cancerous and non-cancerous lung tissue (lack of matched tissue sample control, lack of aneuploidy control), (2) gene amplification does not reliably correlate with increased mRNA levels (Pennica et al., Konopka et al.), and (3) increased mRNA levels do not reliably correlate with increased polypeptide levels (Haynes et al., Gygi et al., Lian et al., Fessler et al., Hu et al., LaBaer, Chen et al., Hanna et al.). In view of this, the skilled artisan would have viewed the gene amplification results as preliminary with respect to the utility of the encoded polypeptides, and would have had to experiment further to reasonably confirm whether or not PRO341 polypeptides can be used as a cancer diagnostic agent.

At the bottom of p. 15 of the Brief, Appellant argues that the examiner applied an improper legal standard. Appellant argues that the evidentiary standard is a preponderance of the totality of the evidence. Appellant urges that in order to overcome the presumption of truth of an assumption of utility, the examiner must establish that it is

more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Appellant urges that the burden of rebuttal does not shift to Appellant until a proper *prima facie* showing of lack of utility is made. From p. 15 to p. 16 of the Brief, Appellant argues that it is not a legal requirement to establish a necessary correlation between an increase in copy number of the DNA and protein expression levels that would correlate to the disease state, nor that it is imperative to find evidence that DNA amplification is necessarily or always associated with overexpression of the gene product. This has been fully considered but is not found to be persuasive. The truth, or credibility, of the assertion of utility has not been questioned. Rather, the rejection sets forth that the assertion of utility is not substantial. The preponderance of evidence supports this position. See Pennica et al., Konopka et al., Chen et al. (who found only 17% of 165 polypeptide spots or 21% of the genes had a significant correlation between polypeptide and mRNA expression levels in lung adenocarcinoma samples), Hu et al. (who reviewed 2286 genes reported in the literature to be associated with breast cancer), LaBaer, Haynes et al., Gygi et al., Lian et al., and Fessler et al. These references, taken into consideration with the disclosure, indicate to the skilled artisan that it is more likely than not that PRO341 polypeptide is not useful as a cancer diagnostic agent.

At pp. 16-17 of the Brief, Appellant criticizes the Pennica et al. and Konopka et al. references relied upon by the examiner. Specifically, Appellant characterizes Pennica et al. as being limited to WISP genes, and does not speak to the correlation of gene amplification and protein expression for genes in general. Appellant argues that

the working hypothesis among those skilled in the art is that there is a correlation between gene amplification and protein overexpression. Appellant points out that there was such a correlation for WISP-1 as disclosed by Pennica et al. Appellant characterizes Konopka et al. as being limited to the abl gene, and not speaking to genes in general. Appellant concludes that the examiner must show evidence that it is more likely than not that the correlation does not exist, and that a *prima facie* case of lack of utility has not been made. This has been fully considered but is not found to be persuasive. Pennica et al. and Konopka et al. are relevant even though they are not reviews of gene amplification for genes in general because they show a lack of correlation between gene amplification and gene product overexpression. The instant case also concerns a single gene. Moreover, the rejection is based on more evidence than just Pennica et al. and Konopka et al. The evidence of record indicates that (1) the initial gene amplification assay only showed a positive result for three out of fourteen lung cancer samples, and did not take into account aneuploidy in cancerous and non-cancerous lung tissue (lack of matched tissue sample control, lack of aneuploidy control), (2) gene amplification does not reliably correlate with increased mRNA levels (Pennica et al., Konopka et al.), and (3) increased mRNA levels do not reliably correlate with increased polypeptide levels in the majority of cases (Haynes et al., Gygi et al., Lian et al., Fessler et al., Hu et al., LaBaer, Chen et al., Hanna et al.).

Near the bottom of p. 17 of the Brief, Appellant argues that Haynes et al. support Appellant's position when they state that there was a general trend between protein expression and transcript levels. This has been fully considered but is not found to be

persuasive because Haynes et al. clearly state "[p]rotein expression levels are not predictable from the mRNA expression levels" (p. 1863, top of left column) and "only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts" (p. 1870, under concluding remarks). Clearly, Haynes et al. are saying that mRNA levels do not predict protein levels, in general.

From pp. 17 to 19 of the Brief, Appellant takes issue with a quote from the final rejection. Appellant urges that the examiner is applying a heightened, legally incorrect, utility standard. Appellant argues that the specification shows that the gene encoding PRO341 was significantly amplified 2.173 to 2.514-fold in three lung tumors. Appellant urges that these values were considered significant based on the declaration of Dr. Goddard. Appellant argue that the examiner's characterization of the amplification as "very small" was without basis or evidence. Appellant argues that the examiner must accept an opinion from a qualified expert. Appellant argues that the fact that 3 out of 14 lung tumor samples tested positive in the gene amplification assay does not make the gene amplification data less significant or spurious. Appellant reasons that some tumor markers are useful for identifying rare malignancies. Appellant argues that such rare tumor markers have great value in tumor diagnosis, prognosis, and classification of tumors. Appellant concludes that it is not relevant to utility whether the PRO341 gene was amplified in three lung tumors or most lung tumors sampled. This has been fully considered but is not found to be persuasive. The gene amplification data presented in the specification were problematic. The control DNA appeared to be from blood rather

than from a matched tissue sample (i.e., healthy lung), while the literature shows that matched tissue samples are the standard (Pennica et al., Konopka et al.). Also, the data were not corrected for aneuploidy, a phenomenon that occurs in cancerous and non-cancerous lung (Sen, Hittelman). Therefore, it is not clear that the reported amplification is significant. Furthermore, the three lung tumor samples in which PRO341 was reported as being amplified were not of the same type. PRO341 tested positive in LT16, LT17, and LT21. These are described in the specification as corresponding to stage IB squamous cell carcinoma, stage IIB squamous cell carcinoma, and stage IIB large cell carcinoma, respectively. Other lung tumor samples of the same types did not test positive for PRO341 gene amplification. Therefore, the relevancy of Appellant's comments regarding rare malignancies is not clear. If PRO341 were amplified in all stage IIB squamous cell carcinomas, for example, but no other lung carcinomas, such would appear to indicate that PRO341 was a significant rare malignancy marker for stage IIB squamous cell carcinoma. However, no such trend was disclosed. The specification does not disclose any special feature, or prognosis, of lung tumors that amplify the PRO341 gene compared to lung tumors that do not amplify the PRO341 gene. It is left to the skilled artisan to determine the significance (if any) of such a difference. Such constitutes the type of further research required to bestow a substantial utility on the claimed invention.

At pp. 19-20, Appellant reviews the Orntoft et al., Hyman et al., and Pollack et al. references, and asserts that they constitute evidence that gene amplification increases mRNA expression levels in general. Appellant characterizes Orntoft et al. as studying

5600 gene transcripts in malignant bladder cancers, and concluding that in general (18 out of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts. Appellant characterizes Hyman et al. as studying over 12,000 genes in breast cancer and concluding that there was evidence of a prominent global influence of copy number changes on gene expression levels. Appellant characterizes Pollack et al. as studying a series of primary human breast tumors and concluding that 62% of highly amplified genes show moderately or highly elevated expression, and DNA copy number influences gene expression across a wide range of DNA copy number alterations, and that on average a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels. This has been fully considered but is not found to be persuasive. Orntoft et al. appear to have looked at increased DNA content over large regions of chromosomes and comparing that to mRNA and polypeptide levels from the chromosomal region. Their approach to investigating gene copy number was termed CGH. Orntoft et al. do not appear to look at gene amplification, mRNA levels and polypeptide levels from a single gene at a time. The instant specification reports data regarding amplification of individual genes, which may or may not be in a chromosomal region which is highly amplified. Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p. 40). This analysis was not done for PRO341 in the instant specification. That is, it is not clear whether or not PRO341 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the relevance of Orntoft et al. is not clear. Also, Orntoft et al. compared genes from non-

invasive transitional cell carcinomas to genes from invasive transitional cell carcinomas. There was no comparison between genes in cancerous versus non-cancerous tissue. Finally, Orntoft et al. could only compare the levels of about 40 well-resolved and focused *abundant* proteins. (See abstract.) It would appear that Appellants have provided no fact or evidence concerning a correlation between the specification's disclosure of *low* levels of amplification of DNA (which were not characterized on the basis of those in the Orntoft publication) and an associated rise in level of the encoded protein. Hyman et al. used the same CGH approach in their research. Hyman et al. found 44% (less than half) of *highly* amplified genes showed overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes were amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. This is direct evidence that it is "more likely than not" that gene amplification does not correlate with increased mRNA expression. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO341 would be correlated with elevated levels of mRNA, much less protein. Hyman does not examine protein expression. Pollack et al. also used CGH technology, concentrating on large chromosome regions showing high amplification (p. 12965). Pollack et al. is similarly limited to *highly* amplified genes which were not evaluated by the method of the instant specification, and did not test for protein expression levels. None of the papers are directed to lung cancer. Importantly, none of

the three papers reported that the research was relevant to identifying probes that can be used as cancer diagnostics. The three papers state that the research was relevant to the development of **potential** cancer therapeutics, but also clearly imply that much further research was needed before such therapeutics were in readily available form. Accordingly, the specification's assertions that the claimed PRO341 polypeptides have utility in the fields of cancer diagnostics and cancer therapeutics are not substantial.

Appellant refers again to the Polakis declaration, and argues that the examiner's criticism of the declaration for failing to provide data is improper. Appellant points to statements in the declaration that Dr. Polakis has identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. At the time of the declaration, Dr. Polakis stated that antibodies were generated to about 30 of the tumor antigen proteins expressed from those transcripts and have used the antibodies to quantify protein levels in cancerous and non-cancerous cells. Dr. Polakis stated that he found a very good correlation between mRNA and protein levels (approximately 80%). Dr. Polakis stated his expert opinion that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein. The Polakis declaration under 37 CFR 1.132 filed 07 July 2004 is insufficient to overcome the rejection of claims 124-126 and 129-131 based upon 35 U.S.C. §§ 101 and 112, first paragraph, for the following reasons. The art provides evidence that increased DNA amplification does not correlate with increased mRNA levels, and that increased mRNA levels do not correlate with increased protein levels in both healthy

and cancerous tissues. Thus, the examiner maintains that one skilled in the art would view the instant gene amplification data as merely preliminary with regard to whether or not mRNA or protein levels of PRO341 are specifically amplified in tumors. Further research would have to be done in order to determine if PRO341 mRNA and protein are amplified and, if so, whether or not the amplification is significant enough to reasonably confirm the usefulness of PRO341 protein as a cancer marker. Thus, the claimed invention does not provide products or services in "currently available" to the public.

From p. 20 to p. 21 of the Brief, Appellant notes that the sale of gene expression chips to measure mRNA levels is a highly successful business. Appellant concludes that the research community believes that the information obtained from the chips is useful (i.e., that it is more likely than not that the results are informative of protein levels). This has been fully considered but is not found to be persuasive. Evidence of commercial success has no bearing on the issue of utility. The research community could just as easily be interested in the gene chips as a way of providing preliminary results, which would then be followed up with actual testing of protein levels.

From p. 21 to p. 22 of the Brief, Appellant addresses the comments made in the final rejection regarding the Orntoft et al., Hyman et al., and Pollack et al. references. Appellant argues that Orntoft et al. studied 1800 genes that yielded an increase or decrease in mRNA expression in two invasive tumors compared to non-invasive papillomas (also tumors), and then mapped them to chromosomal locations. Appellant argues that the chromosomal locations had already been analyzed for amplification via CGH. Appellant argues that Orntoft et al. found that in general areas with strong gain of

chromosomal material contained a cluster of genes having increased mRNA expression. Appellant quotes from Orntoft et al. as stating that a highly significant correlation was observed between the level of CGH ratio change (DNA copy number) and alteration detected by arrays (mRNA levels). Appellant argues that Orntoft et al. studied mRNA relation to protein levels and found a highly significant correlation. Appellant concludes that Orntoft et al. supports Appellant's position that proteins expressed by genes that are amplified in tumors are useful as cancer markers. Appellant also argues that there is no clear relevance of the examiner's concern that PRO341 has not been disclosed as being part of a gene cluster. This has been fully considered but is not found to be persuasive. As discussed above, Orntoft et al. concentrated on regions of chromosomes with strong gains of chromosomal material containing clusters of genes (p. 40). Orntoft et al.'s findings could only be extended to other genes in such clusters. This analysis was not done for PRO341 in the instant specification, and so it is not clear whether or not PRO341 is in a gene cluster in a region of a chromosome that is highly amplified. Therefore, the findings of Orntoft et al. cannot be extended to PRO341. Also, Orntoft et al. compared genes from non-invasive transitional cell carcinomas to genes from invasive transitional cell carcinomas. There was no comparison between genes in cancerous versus non-cancerous tissue. Thus, Orntoft et al. did not find any cancer markers. Furthermore, Orntoft et al. could only compare the levels of about 40 well-resolved and focused *abundant* proteins. (See abstract.) Appellant has provided no fact or evidence concerning a correlation between the specification's disclosure of *low* levels of amplification of DNA (which were not

characterized on the basis of those in the Orntoft publication) and an associated rise in level of the encoded protein. Finally, Orntoft et al. did not study lung cancer.

At p. 22, Appellant argues that the examiner has mischaracterized the methods used by Hyman et al. and Pollack et al. Appellant urges that these papers did not use traditional CGH, but rather did gene-by-gene analysis across all chromosomes. Appellant characterizes Hyman et al. as studying 13,824 clones for gene expression and gene copy number in 14 breast cancer cell lines. Appellant quotes from Hyman et al. regarding their finding that up to 44% of the highly amplified genes were overexpressed compared with only 6% for genes with normal copy number. Appellant further quotes from Hyman et al. regarding the cDNA/microarray technique enables the direct correlation of copy number and expression data on a gene-by-gene basis throughout the genome. Appellant concludes that Hyman et al. performed an analysis on a gene-by-gene basis, and clearly shows that it is more likely than not that a gene which is amplified in tumor cells will have increased gene expression. This has been fully considered but is not found to be persuasive. As discussed above, Hyman et al. found 44% (less than half) of *highly* amplified genes showed overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes were amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. This is direct evidence that it is "more likely than not" that gene amplification does *not* correlate with increased mRNA expression. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner

maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO341 would be correlated with elevated levels of mRNA, much less protein. Also, Hyman et al. did not evaluate lung cancer.

From p. 22 to p. 23 of the Brief, Appellant characterizes Pollack et al. as studying DNA copy number across 6691 mapped human genes in 44 predominantly advanced primary breast tumors and 10 breast cancer cell lines. Appellant quotes from Pollack et al., saying that parallel microarrays measurements of mRNA levels reveal the remarkable degree to which variation in gene copy number contributes to variation in gene expression in tumor cells, and that genome-wide, of 117 high-level DNA amplifications, 62% are found associated with at least moderately elevated mRNA levels and 42% associated with highly elevated mRNA levels. Appellant concludes that the Pollack et al. reference constitutes evidence that it is more likely than not that a gene which is amplified in tumor cells will have increased gene expression. This has been fully considered but is not found to be persuasive. A s discussed above, Pollack et al. also used CGH technology, concentrating on large chromosome regions showing high amplification (p. 12965). Pollack et al. is similarly limited to *highly* amplified genes which were not evaluated by the method of the instant specification, and did not test for protein expression levels. Also, Pollack et al. did not study lung cancer.

From p. 23 to p. 24 of the Brief, Appellant comments upon the examiner's evaluation of the Polakis declaration. Specifically, Appellant argues that the Polakis declaration was submitted to support the position that there is a correlation between mRNA and polypeptide levels, and that the correlation between gene amplification and

mRNA levels had been supported by other evidence. Appellant urges that the opinions in the Polakis declaration are all based on factual findings. Appellant cites case law concerning the examiner's requirement to consider all of the evidence of record anew, and that opinion evidence must be considered. Appellant also points to the utility guidelines as directing the examiner to accept an opinion from an expert. Appellant points to the statement in the Polakis declaration that it is Dr. Polakis' considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates with a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. Appellant concludes that the fact-based conclusions of Dr. Polakis would be considered reasonable and accurate by the skilled artisan. This has been fully considered but is not found to be persuasive. As discussed above, in assessing the weight to be given expert testimony, the examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. (1) In the instant case, the nature of the fact sought to be established is whether or not increased mRNA levels are predictive of increased polypeptide levels. (2) The art provides strong evidence that increased mRNA levels do not correlate with increased protein levels in both healthy and cancerous tissues. See Haynes et al., Gygi et al., Lian et al., Fessler et al., Hu et al., and Chen et al. (3) Dr. Polakis has an interest in the case since he is employed by the assignee. Finally, (4) while Dr. Polakis bases his findings with reference to facts, the facts are not independently provided for the

examiner to draw independent conclusions. For example, it is not clear if any of the tumors were from lung, or how highly amplified the genes were that correlated with polypeptide overexpression. Based on the totality of the evidence, considering it anew, it is maintained that one skilled in the art would view the instant gene amplification data as merely preliminary with regard to whether or not mRNA or protein levels of PRO341 are specifically amplified in lung tumors. Further research would have to be done in order to determine if PRO341 mRNA and protein are amplified and, if so, whether or not the amplification is significant enough to reasonably confirm the usefulness of PRO341 protein as a lung cancer marker. Thus, the claimed invention does not provide products or services in "currently available" to the public, and the asserted utility is not substantial.

From p. 24 to p. 25 of the Brief, Appellant criticizes the Hu et al. reference. Specifically, Appellant criticizes Hu et al. for being based upon a statistical analysis of information from published literature rather than from experimental data. Appellant characterizes Hu et al. as being limited to estrogen-receptor-positive breast tumor only. Appellant criticizes the types of statistical tests performed by Hu et al. Appellant concludes that, based on the nature of the statistical analysis performed in Hu et al., and the fact that Hu et al. only analyzed one class of genes, the conclusions drawn by the examiner are not reliably supported. This has been fully considered but is not found to be persuasive. The asserted utility for the claimed polypeptides is based on a sequence of presumptions. First, it is presumed that gene amplification predicts increased mRNA production. Second, it is presumed that increased mRNA production

leads to increased protein production. Hu et al. is directly on point by showing that the second presumption is incorrect when designating proteins as diagnostic markers for cancer. Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). The instant specification does not disclose that PRO341 mRNA levels are expressed at 10-fold or higher levels compared with normal, matched tissue samples. Therefore, based on Hu et al., the skilled artisan would not reasonably expect that PRO341 protein can be used as a cancer diagnostic. Furthermore, Hanna et al. show that gene amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested empirically. Also, Chen et al. (2002, Molecular and Cellular Proteomics 1:304-313) compared mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas (the same type of cancer for which PRO341 tested positive). Only 17% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen et al. clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (p. 304) and "it is not possible to

predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pp. 311-312). The instant specification does not provide additional information regarding whether or not PRO341 mRNA or polypeptide is overexpressed in lung adenocarcinomas, and thus the skilled artisan would need to perform additional experiments to reasonably confirm such. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial. Regarding Appellant's criticism of Hu et al.'s statistical analysis, Appellant is holding Hu et al. to a higher standard than their own specification, which does not provide proper statistical analysis such as reproducibility, standard error rates, etc. Regarding Appellant's criticism of Hu et al. as being limited to a specific type of breast tumor, Hu et al. is cited as one of several pieces of evidence that gene amplification in a tumor does not correlate with mRNA overproduction or protein overproduction. When viewed with the evidence of record as a whole, there is no correlation between gene amplification, mRNA levels and protein levels. In view of the totality of the evidence, including the declarations submitted under 37 CFR 1.132 and the publications of record, the instant utility rejection is appropriate.

At p. 26 of the Brief, Appellant summarizes the conclusions drawn form the references cited so far. Appellant argues that while there are some examples in the art that do not fit within the central dogma of molecular biology that there is a correlation between polypeptide and mRNA levels, these instances are rare rather than the rule. Appellant urges that in the majority of amplified genes, the evidence (including Orntoft et al., Hyman et al., Pollack et al., the Polakis declaration) shows that gene amplification

influences gene expression at the mRNA and protein levels. Appellant argues that Pennica et al., Konopka et al., and Hu et al. are not sufficient to establish a *prima facie* case of lack of utility since they allegedly don't address correlation of protein levels and gene amplification for genes in general. Appellant characterizes Haynes et al. as supporting Appellant's position that gene amplification mostly correlates well with protein expression because most of the 80 genes showed some positive correlation (Figure 1). Appellant concludes that the examiner has not established that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Appellant argues that one skilled in the art would reasonably expect, based on the gene amplification data, that PRO341 polypeptide is also overexpressed. This has been fully considered but is not found to be persuasive. Regarding Haynes et al., more than 80 polypeptides relatively homogeneous in half-life and expression level were studied, and no strong correlation between polypeptide and transcript level was found. For some genes, equivalent mRNA levels translated into polypeptide abundances which varied more than 50-fold. Haynes et al. concluded that the polypeptide levels cannot be accurately predicted from the level of the corresponding mRNA transcript (p. 1863, second paragraph, and Figure 1). Specifically, Haynes et al. state, "These results suggest that even for a population of genes predicted to be relatively homogenous with respect to protein half-life and gene expression, the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript" (p. 1863, middle of left column). Haynes et al. also state, "[p]rotein expression levels are not predictable from the mRNA expression levels" (p. 1863, top of left column) and "only the direct analysis

of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts" (p. 1870, under concluding remarks). Clearly, Haynes et al. are saying that mRNA levels do not predict protein levels, in general. Regarding the evidence as a whole, first, PRO341 genomic DNA was found to be amplified in only three out of fourteen lung cancer samples compared to a normal DNA control from blood. Gene amplification in lung tumors was not compared to a matched normal tissue sample, as is the standard in the art (see Pennica et al., Konopka et al.). The data were not corrected for aneuploidy, which was known to be common in cancerous and non-cancerous lung tissue (see Sen, Hittelman). Thus, it is not clear from the gene amplification data whether or not PRO341 genomic DNA actually is amplified in certain lung tumors. Second, the literature reports that gene amplification often does not correlate with increased mRNA levels (see Pennica et al., Konopka et al.). Third, the literature reports that increased mRNA levels do not correlate with increased polypeptide levels in healthy tissue (see Haynes et al., Gygi et al., Lian et al., Fessler et al.) or cancerous tissue (see Hu et al., LaBaer, Chen et al., Hanna et al.). In view of the totality of the evidence, the skilled artisan would *not* reasonably presume that PRO341 polypeptide is overexpressed in certain lung tumors based on the disclosure regarding gene amplification without actually testing for PRO341 polypeptide overexpression. The requirement for such testing to reasonably confirm the asserted utility indicates that the asserted utility is not substantial, i.e., it is not in currently available form. In view of the totality of the evidence, the rejections for lack of utility and enablement are proper.

At p. 26 to p. 27 of the Brief, Appellant argues that even if an amplified gene did not correlate with an overexpressed encoded protein, the protein would still have a credible, specific, and substantial asserted utility. Appellant points to the declaration of Dr.. Ashkenazi, submitted under 37 CFR 1.132 on 24 October 2003, as establishing that, even if the protein were not overexpressed, the simultaneous testing of gene amplification and gene product overexpression would enable more accurate tumor classification. Appellant concludes that such a situation would allow for better tumor classification and better determination of suitable therapy. Appellant argues that absence of overexpression is crucial information for a clinician, because it indicates that the patient should not be treated with agents that target that gene product. Appellant argues that this saves money and benefits the patients who can avoid exposure to the side effects associated with such agent. This has been fully considered but is not found to be persuasive. The specification does not disclose such further testing of gene product overexpression. Therefore, the skilled artisan would have been required to do the testing to reasonably confirm whether or no the PRO341 polypeptide is overexpressed. In view of such requirement, the products or services based on the claimed invention are not in "currently available" form for the public. Furthermore, the specification provides no assertion that the claimed PRO341 polypeptides are useful in tumor categorization, nor does it provide guidance regarding what treatment modalities should be selected by a physician depending upon whether or not a tumor overexpresses PRO341. For example, neither the specification nor the prior art discloses an agent that targets PRO341 that is useful for cancer therapy. This is also

further experimentation that would have to be performed by the skilled artisan, indicating that the asserted utility is not substantial.

At p. 27 to p. 28 of the Brief, Appellant argues that the Hanna et al. reference supports the utility of tumor categorization. Appellant characterizes Hanna et al. as disclosing that the HER-2/neu gene is amplified and/or overexpressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinomas. Appellant argues that Hanna et al. disclose that diagnosis of breast cancer includes testing for both amplification of the HER-2/neu gene and overexpression of HER-2/neu gene product. Appellant argues that even when the protein is not overexpressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it. Appellant comments on the examiner's criticism of Hanna et al., stating that the examiner has misread the reference. Appellant argues that Hanna et al. disclose that gene amplification and protein overexpression are well correlated, and that only a subset of tumors show discordant results. Appellant urge that Hanna et al. support Appellant's position that it is more likely than not that gene amplification correlates with increased polypeptide expression. Appellant argues that the IHC is not used to test polypeptide expression levels empirically. Appellant argues that, rather, the screening strategy is for the selection of patients who should receive treatment with Herceptin. Appellant concludes that the purpose of measuring both protein and gene levels is not for further experimentation, but for further characterization of tumors into medically relevant categories. This has been fully considered but is not found to be persuasive. Hanna et al. clearly show that the skilled artisan does not assume that any

tumor with a HER-2/neu gene amplification event also overexpressed HER-2/neu protein. It is tested empirically. The reason for the testing is irrelevant to the issue at hand. The fact remains that the instant specification does not disclose whether or not PRO341 protein is overexpressed in any tumors. Therefore, the skilled artisan must perform further research in order to reasonably confirm whether it is or is not. The requirement for such further research indicates that the asserted utility of PRO341 as a cancer diagnostic agent is not substantial. The specification does not assert that PRO341 is useful as an agent to categorize tumors. However, even if it had, the specification does not disclose the expression levels of PRO341 protein in any tumor samples, so that such would have to be determined through further research on the part of the skilled artisan. Thus, even the utility proposed in the Brief regarding the usefulness of PRO341 protein in the categorization of tumors, is not substantial. Finally, there is no disclosure regarding what treatment modality should be chosen by the clinician based on whether or not PRO341 polypeptide is overexpressed. The determination of such constitutes further experimentation, indicating that the asserted utility is not substantial.

At the top of p. 28 of the Brief, Appellant argues that they have clearly shown that the gene encoding the PRO341 polypeptide is amplified in at least 3 primary lung carcinoma tumors. Appellant urges that the PRO341 gene, similar to the HER-2/neu gene of Hanna et al., is a tumor associated gene. Appellant argues that the majority of amplified genes correlate with increased mRNA and protein levels. Appellant concludes that one skilled in the art would reasonably expect that, based on the gene amplification

data for the PRO341 gene, that the PRO341 protein is concomitantly overexpressed and is useful in tumor categorization. This has been fully considered but is not found to be persuasive. First, PRO341 genomic DNA was found to be amplified in only three out of fourteen lung cancer samples compared to a normal DNA control from blood. Gene amplification in lung tumors was not compared to a matched normal tissue sample, as is the standard in the art (see Pennica et al., Konopka et al.). The data were not corrected for aneuploidy, which was known to be common in cancerous *and non-cancerous* lung tissue (see Sen, Hittelman). Thus, it is not clear from the gene amplification data whether or not PRO341 genomic DNA actually is amplified in certain lung tumors. Second, the literature reports that gene amplification often does not correlate with increased mRNA levels (see Pennica et al., Konopka et al.). Third, the literature reports that increased mRNA levels do not correlate with increased polypeptide levels in healthy tissue (see Haynes et al., Gygi et al., Lian et al., Fessler et al.) or cancerous tissue (see Hu et al., LaBaer, Chen et al., Hanna et al.). In view of the totality of the evidence, the skilled artisan would not reasonably presume that PRO341 polypeptide is overexpressed in certain lung tumors based on the disclosure regarding gene amplification without actually testing for PRO341 polypeptide overexpression. The requirement for such testing indicates that the asserted utility is not substantial, i.e., it is not in currently available form. Fourth, based on the gene amplification data, the skilled artisan *also* would not presume that PRO341 polypeptide is *not* overexpressed in certain lung tumors without actually testing for PRO341 polypeptide levels. In view of such and the lack of guidance regarding how the physician would use information

regarding PRO341 polypeptide overexpression, or lack of overexpression, in categorizing a tumor and choosing a treatment modality, the asserted utility for PRO341 polypeptide as a cancer diagnostic agent is not substantial. In view of the totality of the evidence, the rejections for lack of utility is proper.

From p. 28 to p. 29 of the Brief, Appellant argues that the Ashkenazi declaration and the Hanna et al. reference provide evidence that, even if gene amplification were not to result in overexpression of the encoded polypeptide, analysis of the expression of the polypeptide is useful in determining the course of treatment. Appellant argues that the examiner is incorrect in asserting that such testing involves further characterization of the PRO341 polypeptide itself. Appellant argues that such testing is for the purpose of characterizing the tumors into medically relevant categories. Appellant adds that such testing techniques were routine in the art of clinical oncology at the time of filing of the instant application. This has been fully considered but is not found to be persuasive. First, testing whether or not a polypeptide is overexpressed in a particular tumor yields information regarding the tumor *and* the polypeptide itself. Second, the specification does not assert that PRO341 polypeptide is useful as a tumor categorization agent. Such is only presented in the arguments and declaration. Third, even if such were asserted in the specification as filed, the skilled artisan would still have to perform further research to reasonably confirm whether or not PRO341 polypeptide is overexpressed in any tumor, since the expression levels of PRO341 polypeptide are not disclosed in the specification. The requirement for such further research indicates that the utility is not in currently available form, i.e., it is not

substantial. Finally, it is no small matter to go from information regarding protein expression levels in a tumor to designing a therapeutic regimen specific to the protein expression profile. In Hanna et al., Herceptin was discussed as a drug specific to tumors expressing HER-2/neu. Herceptin had been known prior to the publication of Hanna et al. No such drug is disclosed in the specification, nor in the prior art, regarding the PRO341 polypeptide. Identifying a drug specific for PRO341 would involve more than routine experimentation, as it would require a great amount of experimentation (e.g., screening agents for effects on PRO341 polypeptide and on tumor), considering there is no guidance or working examples relative to such drugs in the specification or the prior art.

At p. 29 of the Brief, Appellant argues that the specification discloses the sequence of PRO341, including sequences comprising epitope tags of Fc regions, step-by-step protocols for making an expressing PRO341 in appropriate host cells, step-by-step protocols for production of antibodies that bind PRO341, and the gene amplification assay. Appellant concludes that the skilled artisan would know how to make and use the claimed polypeptide for the diagnosis of lung carcinoma. Appellant argues that, based on the disclosure and the advanced state of the art in oncology, the skilled artisan would have found such testing routine and not undue. This has been fully considered but is not found to be persuasive. The examiner concedes that the specification teaches how to make PRO341 polypeptide. However, the specification fails to provide a substantial asserted utility for the claimed PRO341 polypeptides, and thus the specification also fails to enable the claimed PRO341 polypeptides

(specifically, the specification fails to teach the skilled artisan how to use the claimed PRO341 polypeptides without undue experimentation). As discussed above, PRO341 genomic DNA was found to be amplified in only three out of fourteen lung cancer samples compared to a normal DNA control from blood. Gene amplification in lung tumors was not compared to a matched normal tissue sample, as is the standard in the art (see Pennica et al., Konopka et al.). The data were not corrected for aneuploidy, which was known to be common in cancerous *and non-cancerous* lung tissue (see Sen, Hittelman). Thus, it is not clear from the gene amplification data whether or not PRO341 genomic DNA actually is amplified in certain lung tumors. Second, the literature reports that gene amplification often does not correlate with increased mRNA levels (see Pennica et al., Konopka et al.). Third, the literature reports that increased mRNA levels do not correlate with increased polypeptide levels in healthy tissue (see Haynes et al., Gygi et al., Lian et al., Fessler et al.) or cancerous tissue (see Hu et al., LaBaer, Chen et al., Hanna et al.). In view of the totality of the evidence, the skilled artisan would not reasonably assume that PRO341 polypeptide is overexpressed in certain lung tumors based on the disclosure regarding gene amplification without actually testing for PRO341 polypeptide overexpression. The requirement for such testing indicates that the asserted utility is not substantial, i.e., it is not in currently available form. Fourth, based on the gene amplification data, the skilled artisan *also* would not presume that PRO341 polypeptide is *not* overexpressed in certain lung tumors without actually testing for PRO341 polypeptide levels. In view of such and the lack of guidance regarding how the physician would use information regarding PRO341

polypeptide overexpression, or lack of overexpression, in categorizing a tumor and choosing a treatment modality, the asserted utility for PRO341 polypeptide as a cancer diagnostic agent is not substantial. In view of the totality of the evidence, the rejections for lack of utility and enablement is proper.

**(11) Related Proceeding(s) Appendix**

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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